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Neonatal early onset group B streptococcal infection. A nine-year retrospective study in a tertiary care hospital

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1 Introduction

The group B streptococcus (GBS, Streptococcus agalactiae) has been one of the leading causes of neonatal infections in the western world since the early 1970s [3, 5, 8]. The incidence of GBS disease varies over different countries, but appears to be constant over the last fifteen years [6]. GBS infections can have an early or a late onset, each of which is associated with a distinct clinical picture.

Early-onset disease (EOD) occurs in the first seven days of life and is usually caused by vertical transmission from the birth canal. Of all pregnant women, 4–40% are colonized with GBS, depending on the population, the sample sites and culture methods [4, 6, 9, 12]. The rectum is the main reservoir, which often contaminates the vagina [9, 11]. Transmission during labor occurs in 28–73%, but only 1–5% of colonized infants develop EOD [2, 12]. The incidence amounts to 0.7–3.7/1000 live births [6]. Low birth weight, preterm delivery, prolonged rupture of membranes, signs of intrapartum infection, heavy colonization and multiple birth have been noted to be risk factors for EOD [3, 8]. Infants of mothers with low levels of serogroup-specific antibodies against GBS also have a higher risk to develop disease [6]. The most common manifestation of EOD is respiratory disease, which may resemble the clinical picture of hyaline membrane disease [14]. Other manifestations are sepsis, meningitis, jaundice and lethargy, but the infection may be asymptomatic as well [5]. The prognosis of EOD seems to have improved over the years: older studies report mortality rates of 50–80%, while rates of 13–37% are reported more recently [6].

Late-onset disease (LOD) occurs after seven days of age and is caused by both vertical transmission and nosocomial contact [3, 6]. The incidence of LOD amounts to 0.8–1.9/1000 live births [3, 6]. LOD more often presents as meningitis (85%) and sepsis, as well as local infections, including osteoarthritis, urinary tract infection, pneumonia and cellulitis [6, 14]. LOD has a mortality rate of 0–23% [3, 14]. Unfortunately, approximately 50% of GBS-meningitis survivors will develop neurological damage [7].

Curriculum vitae

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In this study, all patients with neonatal GBS infection admitted to the neonatal intensive care unit of our hospital between 1985 and 1993 were reviewed to verify the tendency of decreasing mortality described by others, as well as to establish the long-term outcome in relation to prognostic and fisk factors.

2 Material and methods

The data of all patients with a GBS-positive blood or cerebrospinal fluid culture, as well as patients with clinical symptoms and either positive superficial (ear, nose, throat, umbilicus) or maternal cervical culture were rewiewed.

Maternal fever $\geq 38\,^{\circ}C$, leucocytosis ($> 16 \times 10^9$/liter) and/or fetal tachycardia of > 160 beats per minute were regarded as intrapartum signs of infection. Gestational age, duration of membrane rupture, birth weight, sex, 5 minute Apgar score, clinical and laboratory findings, treatment and clinical outcome at the age of at least one year were recorded. To determine outcome, data from the latest visit to the out-patient clinic were used or a questionnaire was sent to the parents.

3 Results

3.1 Frequency and mortality

EOD was diagnosed in 78 patients (41 males, 37 females). In 61, there were both symptoms and a positive blood culture. A positive blood culture without symptoms was found in 14 patients. Three patients had no positive blood culture but clear symptoms; two of them were treated with antibiotics before culturing. In 8 of the 78 patients other microorganisms were cultured from blood as well: Escherichia coli (3), Staphylococcus aureus (3), viridans streptococci (1) and Klebsiella pneumoniae plus Proteus mirabilis (1). All these eight patients had symptoms of infectious disease. All five patients in whom cerebrospinal fluid cultures were GBS-positive died.

In figure 1 the distribution of cases and mortality over the years is shown. The number of newborns with EOD varied from 4 to 14 per year. Overall mortality rate was found to be 23%.

LOD occurred in four patients (2 males, 2 females). Two patients, both with meningitis, died and the other two survived without sequelae. They were not further included into this study.

3.2 Clinical presentation

Fourteen patients with EOD (18%) had a positive blood culture without clinical symptoms. In all remaining 64 cases of EOD, manifestations occurred within the first 48 hours. These were a variety of combinations of respiratory disease (53%), persistent pulmonary hypertension (16%), shock (13%), convulsions (12%), hyperbilirubinemia (9%), signs of necrotizing enterocolitis (8%), apnoea and bradycardia (5%), hypotonia (5%), cyanosis (3%) and oedema (3%). Laboratory findings consisted of leucocytosis, thrombopenia, leucopenia, hyperglycemia, metabolic acidosis and elevated C-reactive protein.

3.3 Treatment

Treatment consisted of intravenous administration of a β-lactam antibiotic (ampicillin, amoxicillin or a third generation cephalosporin) in combination with an aminoglycoside (mostly gentamicin). In some cases, patients were treated with a penicillin-derivative only, including amoxicillin/clavulanic acid. In a number of cases, administration of antibiotics was changed from intravenous into oral after a few days.

3.4 Risk factors

The presence of risk factors and related mortality were reviewed in all patients with EOD (table I). Half of the patients had a gestational age below 37 weeks. Of all fatal cases, 61% was below 37 weeks. Remarkably, no mortality was found in the group between 34−37 weeks. Thirty-two patients (41%) had a birth weight below 2500 g, and 35% of them died. GBS-infection was not related to fetal growth retardation, since the population showed a normal distribution over the birth weight percentiles (figure 2) [10]. Thirty-eight patients had a birth weight below and 40 above the 50th percentile.

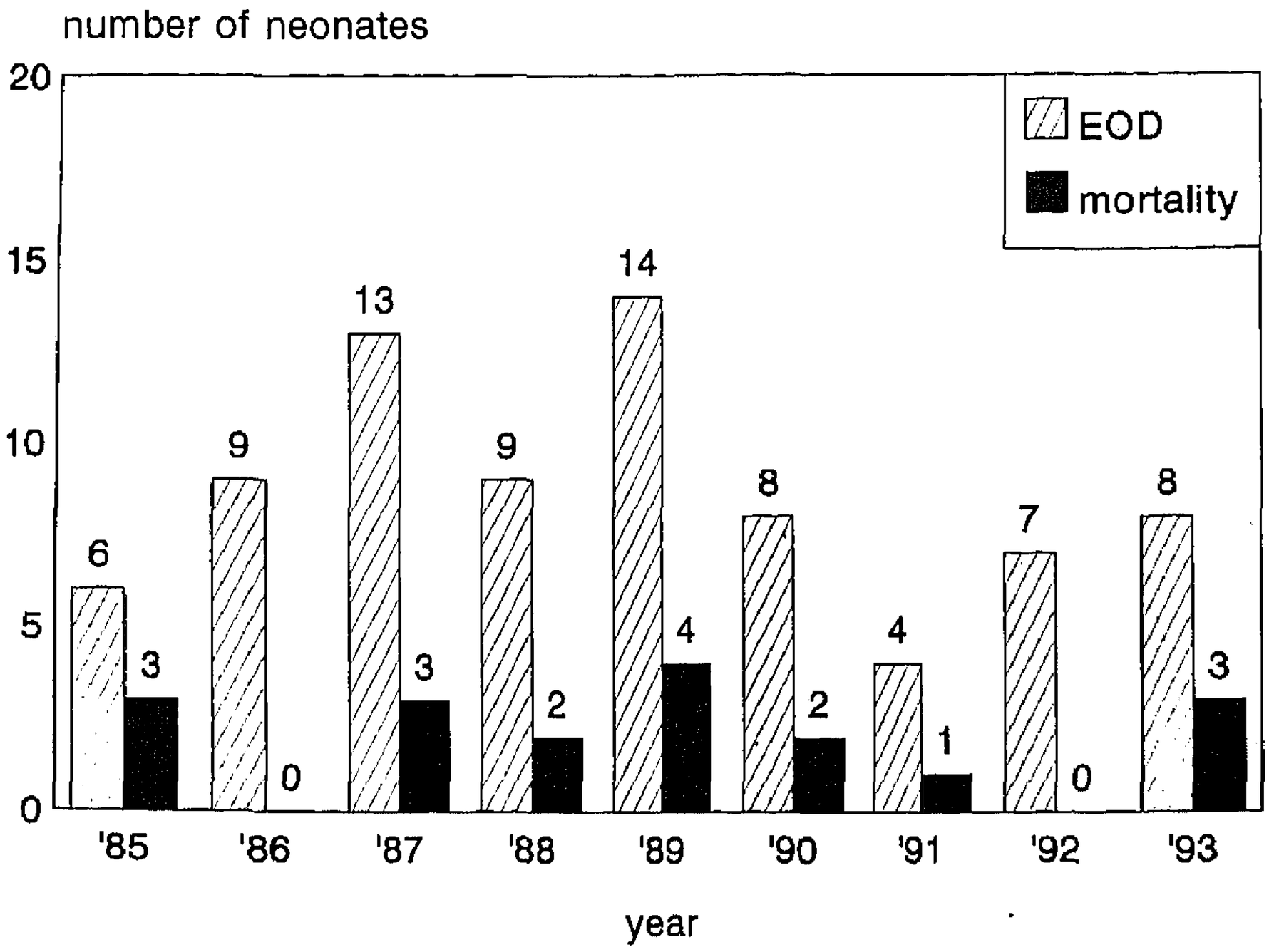

Figure 1. Number of neonates per year with GBS early onset disease (EOD) and related mortality.

Table I. Most important risk factors* in 78 cases of neonatal GBS early onset disease and related mortality

Parameter		GBS early onset disease (%)	Mortality (%)
Gestational age	26–28 weeks	8 (10)	5 (28)
	28–34 weeks	20 (26)	6 (33)
	34–37 weeks	12 (15)	0
	≥37 weeks	38 (49)	7 (39)
Duration of ruptured membranes	0–12 hours	16 (20)	7 (39)
	12–24 hours	16 (20)	6 (33)
	24–48 hours	21 (27)	0
	≥48 hours	18 (23)	4 (22)
	unknown	7 (9)	1 (6)
Intrapartum signs of infection**	absent	46 (59)	6 (33)
	present	29 (37)	12 (67)
	unknown	3 (4)	0
Number of risk factors* present	0	13 (17)	4 (22)
	1	24 (30)	8 (44)
	2	16 (21)	0
	3	15 (19)	4 (22)
	unknown	10 (13)	2 (12)

* Most important known risk factors from the literature: preterm delivery (< 37 weeks), prolonged rupture of membranes (>24 hours before delivery), and intrapartum maternal fever.
** Maternal temperature ≥ 38 °C, , and/or maternal leucocytosis > 16 × 10^9/l, and/or fetal tachycardia > 160 beats/min.

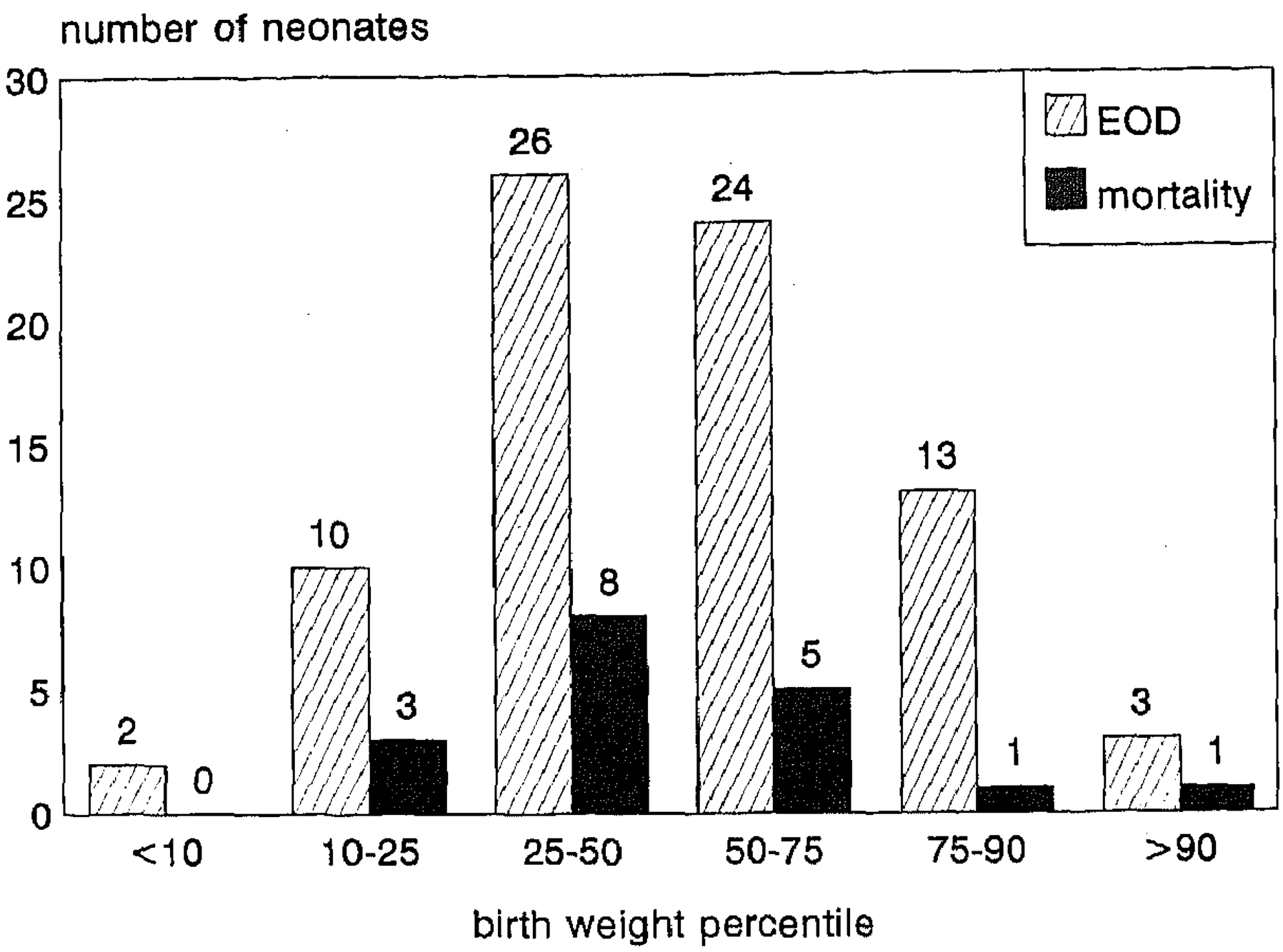

Figure 2. Number of neonates with GBS early onset disease (EOD) and related mortality by birth weight percentile [10].

Prolonged rupture of membranes (> 24 hours) was present in at least 50% of all cases; duration was unknown in 9%. Signs of intrapartum infection were present in over one third of all cases (37%).

Data about risk factors were incomplete in 10 patients; however, 5 of them had at least one risk factor. Therefore, at least one risk factor was present in 82% of the cases (60/73). This leaves about one out of five patients without any of the three risk factors studied.

3.5 Follow-up

In 44 of the 60 survivors (73%) long term follow up data of at least one year were available. Fourteen parents did not return the questionnaire, two families had moved and could not be located. Thirty of these 44 patients (68%) had no sequelae. Unfortunately, one of them suffered from Hemophilus influenzae meningoencephalitis at the age of 10 months, which left him severely handicapped. Three patients suffered from spastic tetraplegia, one of them also showed mental retardation. Two patients had a combination of spastic diplegia and congenital strabismus. Logopedia was indicated for three patients, one of them never had symptoms of GBS-sepsis. Neuromotor developmental delay was present in four patients, one of them also had problems with speech and social development. One patient had behavioral problems and EEG disturbances and one had absences at a very young age.

Table II shows the outcome in the 78 patients with EOD. Mortality was higher in neonates with lower gestational age (< 34 weeks: 39% vs ≥ 34 weeks: 14%) with more sequelae among the survivors with known outcome (44% vs 25%). In neonates with a gestational age of ≥ 37 weeks, the mortality rate was 19% and sequelae were found in 24% of survivors with known outcome. Of the 32 patients born within 24 hours after the membranes had ruptured 13 died (41%), and 6 of the 13 patients with known outcome had sequelae (46%). Thirty-nine patients were born after prolonged rupture of membranes, 4 (10%) died, and 7 of 27 patients with known outcome (26%) had sequelae. The presence of intrapartum signs of infection did not increase the mortality rate, but doubled the frequency of sequelae in survivors with known outcome (47% vs 23%). Survivors with known outcome, born by caesarean section,

had more sequelae (58%) than those born by instrumental or spontaneous delivery (27%). Among neonates with a 5 minute Apgar score < 7 the mortality rate was higher (31%) than in the group with a score ≥ 7 (21%). Two thirds of survivors in the low Apgar score group had sequelae versus 23% in the high Apgar score group. Eleven of 26 surviving patients (42%) with symptoms of GBS-infection within one hour after birth had sequelae. Nine of them were severely damaged. Two of five surviving patients with symptoms between one and six hours after birth had (minor) sequelae. Among the four surviving patients with symptoms occurring after six hours and known outcome, no sequelae were found. Early treatment, within one hour after birth, resulted in less mortality, but did not influence the outcome in survivors. All patients with spastic

Table II. Presence of some parameters and related outcome of 78 neonates with GBS early onset disease

Parameter		N	Mortality (%)	Permanent sequelae in survivors		
				unknown (%)	no (%)	yes (%)
Gestational age	<28 weeks	8	5 (62)	–	2 (67)	1 (33)
	28–34 weeks	20	6 (30)	1 (7)	7 (50)	6 (43)
	34–37 weeks	12	–	5 (42)	5 (42)	2 (16)
	≥37 weeks	38	7 (19)	10 (32)	16 (52)	5 (16)
Duration of ruptured membranes	<24 hours	32	13 (41)	6 (32)	7 (36)	6 (32)
	≥24 hours	39	4 (10)	8 (23)	20 (57)	7 (20)
	unknown	7	1 (14)	2 (33)	3 (50)	1 (17)
Intrapartum signs of infection*	absent	46	12 (26)	8 (24)	20 (59)	6 (17)
	present	29	6 (21)	8 (35)	8 (35)	7 (30)
	unknown	3	–	–	2 (67)	1 (33)
Mode of delivery	spontaneous	47	13 (28)	8 (24)	19 (56)	7 (20)
	instrumental	10	–	4 (40)	6 (60)	–
	c. section	21	5 (24)	4 (25)	5 (31)	7 (44)
5 min. Apgar score	< 7	13	4 (31)	–	3 (33)	6 (67)
	≥ 7	65	14 (21)	16 (31)	27 (53)	8 (16)
Onset of symptoms**	< 1 h postpartum	45	11 (24)	8 (24)	15 (44)	11 (32)
	1– 6 h postpartum	7	2 (29)	–	3 (60)	2 (40)
	6–12 h postpartum	2	1 (50)	–	1 (100)	–
	12–24 h postpartum	7	3 (43)	2 (50)	2 (50)	–
	24–48 h postpartum	3	1 (33)	1 (50)	1 (50)	–
Start of treatment	< 1 h postpartum	34	1 (3)	9 (27)	15 (46)	9 (27)
	1– 6 h postpartum	9	6 (67)	–	2 (67)	1 (33)
	6–12 h postpartum	15	5 (33)	1 (10)	6 (60)	3 (30)
	12–24 h postpartum	5	3 (60)	1 (50)	1 (50)	–
	24–48 h postpartum	10	3 (30)	3 (43)	3 (43)	1 (14)
	≥48 h postpartum	5	–	2 (40)	3 (60)	–

* Maternal temperature ≥ 38 °C, and/or maternal leucocytosis > 16×10^9/l, and/or fetal tachycardia >160 beats/min.

** 14 neonates with GBS-positive blood culture did not develop clinical symptoms as early treatment was started because of signs of infection in the mother and/or laboratory findings.

disorders were preterm. Three of four patients with neuromotor developmental delay were over 37 weeks of gestational age. All eight patients with positive cultures of other microorganisms besides GBS survived.

4 Discussion

To reduce adverse outcome of early onset GBS-disease, early identification and treatment is essential. We could not prove any decrease in mortality rate of infants with EOD during the last ten years in our population. Prematurity, prolonged rupture of membranes and antenatal signs of infection were confirmed as risk factors. Birth weight was not found to be an independent risk factor, but reflected gestational age. Absence of risk factors does not ecxlude EOD, since almost 20% of patients had none of the studied risk factors. In all cases of neonatal disease of unknown origin, GBS-sepsis should be included in the differential diagnosis.

As 14 patients were treated because of GBS-positive blood culture before any symptoms developed, their inclusion in the study can be debated. The possibility of contamination of blood cultures collected from a peripheral vene, and especially from umbilical vessels or catheters, cannot be totally excluded [13]. If they would not have developed EOD without treatment, their inclusion would be incorrect. Then, the prognosis of EOD in this study would be worse.

The outcome in the group of neonates born after prolonged rupture of membranes was not unfavorable, probably due to a higher degree of alertness to GBS-disease. Patients born by ceasarean section had more sequelae, which can probably be explained by fetal distress being the reason for emergency caesarean section.

It is difficult to predict outcome of GBS-sepsis in individual cases. Sequelae cannot always be exclusively related to GBS-sepsis, especially in preterm infants. Outcome is also determined by the occurrence of other disorders such as cerebral hemorrhage and periventricular leucomalacia. Prematurity and sepsis are both risk factors for intraventricular hemorrhage and periventricular leucomalacia, while maternal GBS colonization has been associated with preterm birth [1]. In our population, all patients with spastic disorders had intraventricular hemorrhage or periventricular leucomalacia, and all were premature.

In conclusion, outcome of GBS-sepsis is influenced by many factors, including gestational age, onset of symptoms and time of treatment, severity of respiratory and circulatory disease and the occurrence of complications related to prematurity. Alertness to the presence of GBS disease is mandatory for early treatment and good outcome.

Abstract

Retrospectively, morbidity and mortality of neonatal early onset group B streptococcal (GBS) infection were established. Risk factors and prognostic factors were determined. Between 1985 and 1993, 78 patients with early onset GBS disease were identified. The overall mortality rate was 23%. In 60 of 73 cases (82%) at least one of the investigated risk factors was present. Low birth weight was not an independent risk factor. Outcome of 44 of 60 survivors (73%) at the age of at least one year was obtained. Almost 30% of them had sequelae. The most important were spastic disorders and delayed psychomotor development. In 42% of patients with symptoms of GBS-infection within six hours after birth sequelae occurred. There were no sequelae among patients with symptoms after 6 hours. All 9 severely brain damaged infants showed symptoms shortly after birth. Mortality and adverse outcome rate were higher in infants with low gestational age or low 5 minute Apgar scores. Early treatment resulted in less mortality, but not in less sequelae.
GBS-sepsis still causes significant mortality and leaves a substantial number of survivors damaged. Alertness to GBS-infection, even in the absence of risk factors, remains crucial for early treatment and good outcome.

Keywords: Neonatal intensive care units, neonatal mortality, newborn, prognosis, risk factors, septicemia, Streptococcus agalactiae.

Zusammenfassung

Früh einsetzende neonatale Infektion mit Streptokokken der Gruppe B. Eine retrospektive Studie über neun Jahre in einer Universitäts-Klinik

Wir berichten retrospektiv über alle Fälle von bewiesener GBS-Sepsis, die in der Zeit zwischen 1985 und 1993 auf der neonatalen Intensivstation des Universitäts-Krankenhauses aufgetreten sind. Die Studie wurde durchgeführt, um die Morbidität und Mortalität von neonataler früh einsetzender Infektion mit Streptokokken der Gruppe B (GBS) festzustellen. Außerdem wurden sowohl Risikofaktoren wie prognostische Faktoren ermittelt. Wir erwarben Patientendaten nach mindestens einem Jahr aus den medizinischen Berichten oder via eines Fragebogens, den wir den Eltern schickten.

Es wurden achtundsiebzig Patienten mit früh einsetzender GBS-Erkrankung identifiziert. Die totale Mortalität betrug 23%. Alle 5 Patienten (6,5%), die die Symptome einer Meningitis zeigten, starben. In 60 der 73 Fälle (82%) war mindestens einer der untersuchten Risikofaktoren (Frühgeburtlichkeit, Zeichen von Infektion während der Entbindung und länger zurückliegender Blasensprung) vorhanden (Table 1). Niedriges Geburtsgewicht war kein unabhängiger Risikofaktor (Fig. 2). Wir erhielten Patientendaten von 44 der 60 Überlebenden (73%) (Table II). Fast 30% von ihnen hatte Folgesymptome. Die wichtigsten davon waren spastische Leiden und eine verzögerte psychomotorische Entwicklung. Bei 42% der Patienten mit Symptomen der GBS-Infektion innerhalb von 6 Stunden nach der Geburt traten Folgesymptome auf. Es wurden keine Folgesymptome in der Patientengruppe, bei der die Infektionssymptome nach einem Intervall von mehr als 6 Stunden nach der Geburt auftraten, festgestellt. Alle 9 Neugeborenen mit schwerer Gehirnschädigung zeigten die Symptome kurz nach der Geburt. Mortalität und die Rate der ungünstigen Krankheitsverläufe waren höher bei Frühgeborenen und Kindern, die einen niedrigen (< 7) Apgar-Score nach 5 Minuten hatten. Frühe Behandlung resultierte in niedrigerer Mortalität, reduzierte jedoch nicht die Folgesymptome. GBS-Sepsis verursacht noch immer eine signifikante Mortalität und hinterläßt eine erhebliche Anzahl von Überlebenden mit Schäden. Wachsamkeit in Bezug auf GBS-Infektion, selbst wenn Risikofaktoren nicht vorhanden sind, bleibt entscheidend für eine frühe Behandlung und bessere Resultate.

Schlüsselwörter: Neonatale Intensivstation, neonatale Mortalität, Neugeborene, Prognose, Risikofaktoren, Sepsis, Streptococcus agalactiae.

Résumé

Infections néonatales précoces à stréptocoque du groupe B. Une étude rétrospective sur neuf ans dans un centre hospitalier universitair

On a passé en revue rétrospectivement tous les cas prouvés de septicémie à stréptocoque du groupe B (GBS) précoce dans une unité de soins intensifs néonatals entre 1985 et 1993 pour determiner la morbidité et mortalité. En outre, nous avons evalué les facteurs de risque de même que les facteurs prognostiques. Les données supplémentaires ont été obtenues par des dossiers médicaux ou par une questionnaire rempli par les parents.

Soixante-dix-huit patients souffrants de GBS précoce ont été identifié. Le taux de mortalité total était de 23%. Tous les 5 patients (6,5%) souffrants de méningite sont morts. En 60 cas sur 73 (82%) au moins un des facteurs de risque examinés à été présent: prématurité, des symptômes d'infection pendant la grossesse et une rupture prolongée des membranes (tableau I). Le faible poids à la naissance n'était pas un facteur de risque indépendant (fig. 2). Nous avons obtenu des données supplémentaires sur 44 des 60 survivants (73%) après au moins un an (tableau II). A peu près 30% d'entre-eux souffrait de suites: les plus importantes étaient des spasticités et développement psychomoteur retardé. Dans 42% des patients qui montraient des symptômes d'infection GBS dans les premiers 6 heures après la naissance, se sont présentés des suites. Il n'y avait pas de suites parmi les patients ou se sont présentés des symptômes après 6 heures. Tous les 9 enfants avec endommagement cérebral sévère montraient des symptômes peu après la naissance. La mortalité et le taux des séquels étaient supérieurs parmi les enfants nés prématurément ou avec un score d'Apgar à 5 minutes moins de 7. Le traitement prompt a fait baisser la mortalité, mais n'a pas réduit les séquels.

La septicémie GBS provoque toujours une mortalité significative. En même temps, parmi les survivants un nombre substantiel reste endommagé.

Il est crucial de rester vigilant à l'infection GBS pour assurer le traitement prompt et pour avoir des bons résultats.

Mots-clés: Facteurs de risque, mortalité néonatale, nouveau-né, prognostic, septicémie, Streptococcus agalactiae, unité de soins intensifs néonatals.

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